FDA Introductory Remarks: Sofosbuvir NDA 204671

Debra Birnkrant, MD
Director, Division of Antiviral Products

Antiviral Drugs Advisory Committee Meeting

October 25, 2013

Silver Spring, MD

Background

- Chronic Hepatitis C (CHC) is a global problem
  - ~ 170 million infected worldwide
- CHC is a domestic problem
  - ~ 3.2 million of the US population are chronically infected
  - Incidence of infection in US is decreasing but CHC related complications are increasing: cirrhosis, HCC
    - With aging of infected population, more liver related complications are expected in the next 10 – 20 years
- CHC already the most common reason for liver transplant

Standard of Care (SOC)*

- GT 1 CHC
  - Protease inhibitor plus pegylated interferon with ribavirin (PEG/RBV)
  - Based on databases supporting approvals of boceprevir and telaprevir
  - Treatment duration variable for GT 1
    - based on RGT
- GT 2,3 CHC
  - Pegylated interferon and ribavirin for 24 weeks

- Response rates depend on multiple factors
  - Some of these factors may be more or less important with DAA regimens, e.g. Q80K viral polymorphism

- Toxicities seen with boceprevir and telaprevir beyond those seen with PEG/RBV

- Important drug interactions seen with PI plus PEG/RBV

*AASLD Treatment Guidelines, 2009, 2011

Challenges for Future DAA Therapy

- Simple regimens
  - Short duration
- Easy dosing
  - Low pill burden, limited drug interactions
- All oral
- Effectiveness across HCV genotypes/subtypes
  - Difficult-to-treat populations
- Safe and tolerable
  - Manageable side effect profile

Sofosbuvir

- Nucleotide inhibitor of HCV NS5B RNA-dependent RNA polymerase
- Broad genotypic activity
- Four pivotal phase 3 trials initially submitted in NDA
  - Studied in multiple populations including interferon ineligible, intolerant; not studied in a PI failure population
  - Control arms variable and population dependent
  - VALENCE study recently submitted that examined longer durations of an IFN-free treatment regimen in GT 3 population
    - Decreased relapse rates in GT 3
- Limited drug interactions
- Well tolerated
- Designated as a Breakthrough Therapy under FDASIA, Title IX as part of an interferon-free regimen in the treatment of CHC

Draft Guidance for Industry: *Chronic Hepatitis C Virus Infection: Developing DAAs for Treatment (Reissued October 2013)*

- **Placebo control design -** placebo group receives the investigational agent after 12-24 weeks (essentially delayed treatment)
- Shorter treatment durations (e.g., 12-24 weeks) make it acceptable to include a placebo control (to defer treatment for a period) **(POSITRON - IFN ineligible, etc.)**
- Primary purpose to allow a **safety comparison** because virologic response for placebo is expected to be zero

- **Historical control design -** recommending historical controls for an all-DAA regimen or regimens with much shorter duration than approved standard of care **(NEUTRINO – 12 weeks SOF+PEG/RBV)**
  - Expectation was that even a lower response rate than an approved option may be acceptable in the setting of an IFN-free regimen or one that significantly shortened the duration of IFN
  - Blinding could also be an issue

Breakthrough Therapy Designation

- Food and Drug Administration Safety and Innovation Act (FDASIA), signed July 2012
- Four expedited programs:
  - Accelerated Approval (1992)
  - Priority Review (1992)
  - Fast Track Designation (1997)
  - Breakthrough Therapy Designation (2012)
- Features
  - All of Fast Track features
  - Intensive guidance on efficient drug development
  - Organizational commitment

Breakthrough Therapy Designation

- Criteria
  - Serious Condition
  - Preliminary clinical evidence demonstrates substantial improvement over available therapy on one or more clinically significant endpoints
    - Greater response rate
    - Important safety advantage
    - Treats the underlying disease or reverses disease progression

Sofosbuvir: FDA Presentation

- Highlights of the clinical program
  - Treatment duration in different populations
    - GT 2,3 naïve (FISSION, POSITRON, VALENCE)
    - GT 2,3 experienced (FUSION, VALENCE)
    - GT 1,4,5,6 (NEUTRINO)
  - Impact of baseline factors on treatment response
    - Exploratory analyses for effectiveness of SOF in genotype 1 PEG/RBV treatment failures
  - Use in HCC patients meeting Milan criteria awaiting liver transplant
  - Treatment emergent resistance assessment
    - Next Generation Sequencing data reviewed
  - Safety assessment
    - Cardiac, other
  - Clinical pharmacology
    - DDI data

AC Questions

- Risk/Benefit of sofosbuvir
  - GT 2,3
  - GT 1,4
    - PEG/RBV treatment-experienced GT 1
- Use of sofosbuvir plus ribavirin in HCC patients meeting Milan criteria and awaiting transplant
- Additional studies

Agenda

8:00 am – 8:15 am	**Call to Order and Introduction of Committee**	**Yoshihiko Murata, MD, PhD Chair, Antiviral Drugs Advisory Committee**
8:15 am - 8:30 am	**Conflict of Interest Statement**	**Karen Abraham-Burrell, PharmD Designated Federal Officer**
8:30 am – 8:45 am	**FDA Introductory Remarks**	**Debra Birnkrant, MD Director, Division of Antiviral Products**
8:45 am – 10:15 am	**Sponsor Presentations**	**Gilead Sciences, Inc.**
10:15 am – 10:30 am	**Clarifying Questions**	
10:30 am – 10:45 am	**BREAK**	
10:45 am - 11:45 am	**FDA Presentations**	**Poonam Mishra, MD and Karen Qi, PhD**
11:45 am – 12:00 pm	**Clarifying Questions**	
12:00 pm – 1:00 pm	**LUNCH**	
1:00 pm – 2:00 pm	**Open Public Hearing**	
2:00 pm – 3:00 pm	**Questions to the Committee/Committee Discussion**	
3:00 pm – 3:15 pm	**BREAK**	
3:15 pm - 5:00 pm	**Questions to the Committee/Committee Discussion**	
5:00 pm	**ADJOURNMENT**	

Sofosbuvir
NDA 204671
FDA Analyses

Poonam Mishra, MD
on behalf of the
Sofosbuvir Review Team

Antiviral Drugs Advisory Committee Meeting
October 25, 2013

Presentation Outline

- Background
- Efficacy Results
  - Primary endpoints
  - Relapse rates
- Pre-Transplant Population
- Clinical Safety
- Clinical Virology
- Clinical Pharmacology
- Genotype 1 PEG/RBV Treatment-Experienced Population

Sofosbuvir (GS-7977)

- Prodrug of a nucleotide analog inhibitor of the hepatitis C virus (HCV) NS5B RNA-dependent RNA polymerase
- First-in-class submission
- Proposed indication: in combination with other agents for treatment of chronic hepatitis C (CHC) in adults
- Sofosbuvir was studied in combination with ribavirin for genotypes 2 and 3, and in combination with pegylated interferon and ribavirin for genotypes 1, 4, 5 and 6.

Efficacy Results

Genotypes 2 and 3

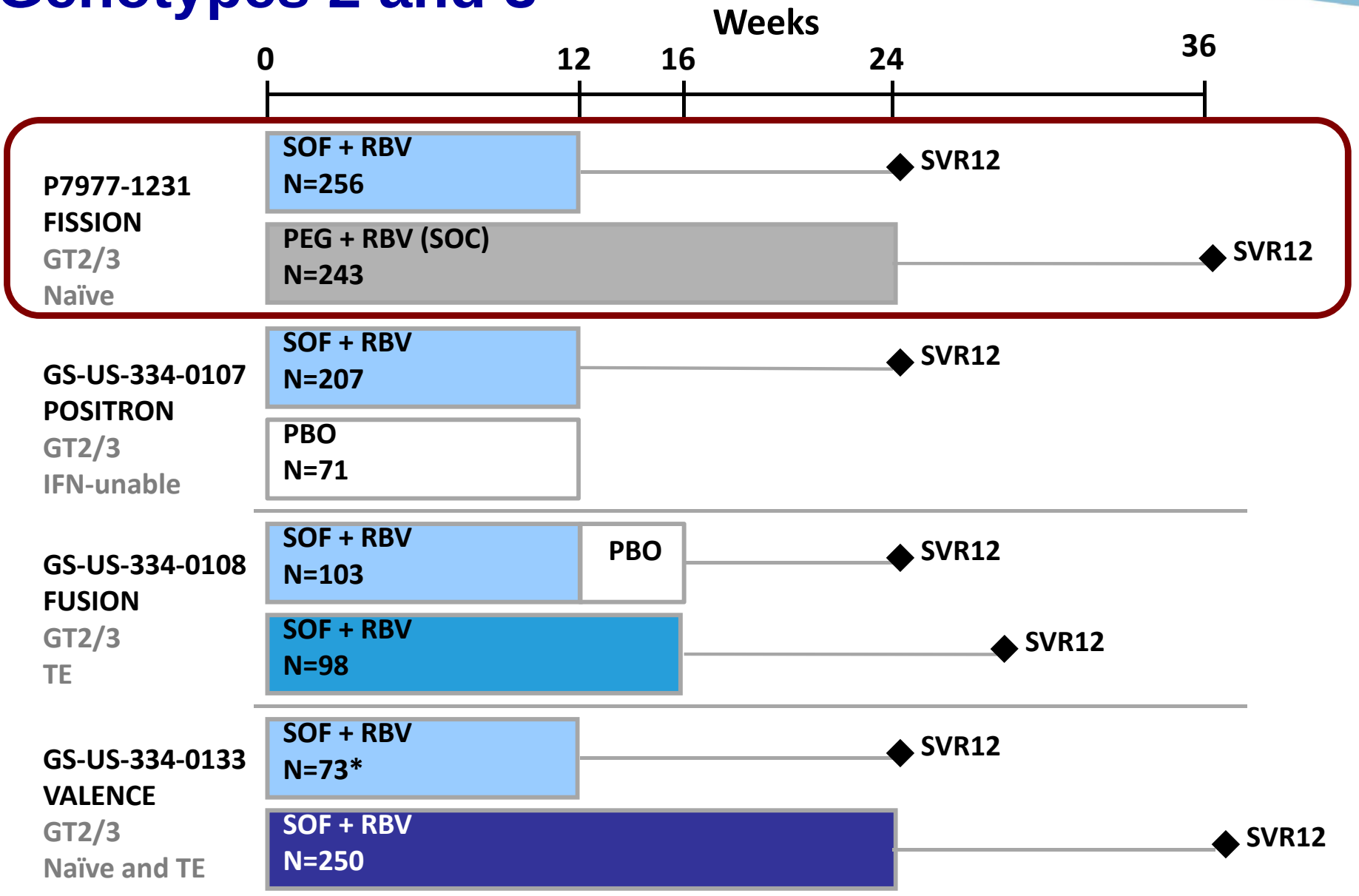
Phase 3 Trials in Genotypes 2 and 3

Trial Name	Population	Regimen* and Duration	Comparator
P7977-1231 (FISSION)	Treatment-Naïve (TN)	SOF+RBV 12 Weeks	PEG/RBV 24 Weeks
GS-US-334-0107 (POSITRON)	IFN-Unable	SOF+RBV 12 Weeks	Placebo
GS-US-334-0108 (FUSION)	Treatment-Experienced (TE)	SOF+RBV 12 Weeks SOF+RBV 16 Weeks	-
GS-US-334-0133 (VALENCE)	TN/TE	GT 2: SOF+RBV 12 Weeks GT 3: SOF+RBV 24 Weeks	-

**Sofosbuvir (SOF) dose was 400 mg once daily and ribavirin (RBV) dose was weight-based (1000 or 1200 mg daily doses)*

SVR12 was the primary endpoint in all clinical trials

Phase 3 Trial Designs: Genotypes 2 and 3

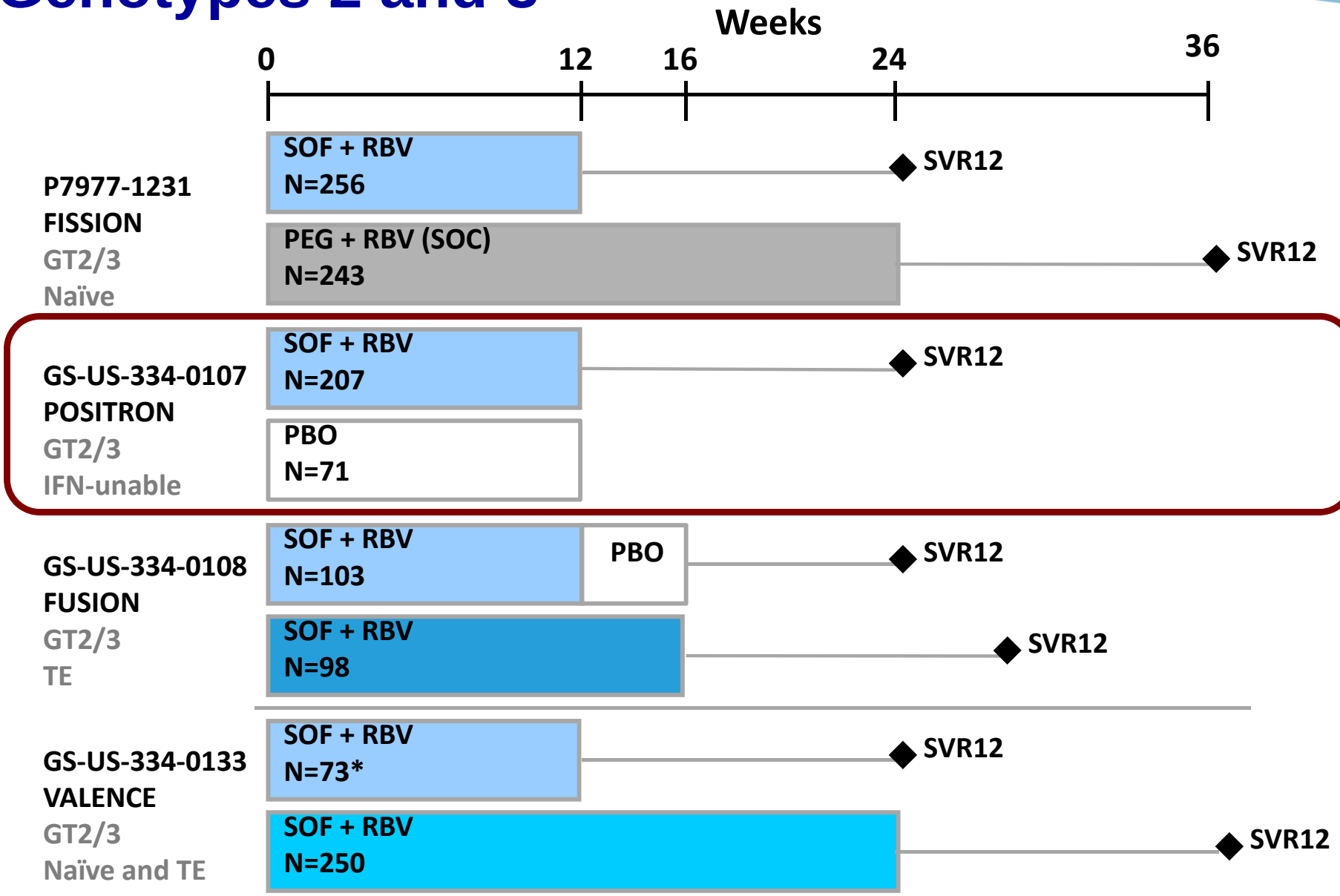


N=Number of subjects; SOC=Standard of care; PBO=Placebo; *N represents GT2 subjects only

FISSION: GT 2/3 Treatment-Naive SVR12 and Relapse Rates

	SOF+RBV 12 Weeks N=256	PEG/RBV 24 Weeks N=243
Overall SVR12	**67%**	**67%**
Treatment Difference (95% CI)	0.1% (-8%, 8%)	
GT 2	**95%** (69/73)	**78%** (52/67)
GT 3	**56%** (102/183)	**63%** (110/176)
Overall Relapse Rate	**30% (76/252)**	**21% (46/217)**
GT 2	**5%** (4/73)	**15%** (9/62)
GT 3	**40%** (72/179)	**24%** (37/155)

Phase 3 Trial Designs: Genotypes 2 and 3

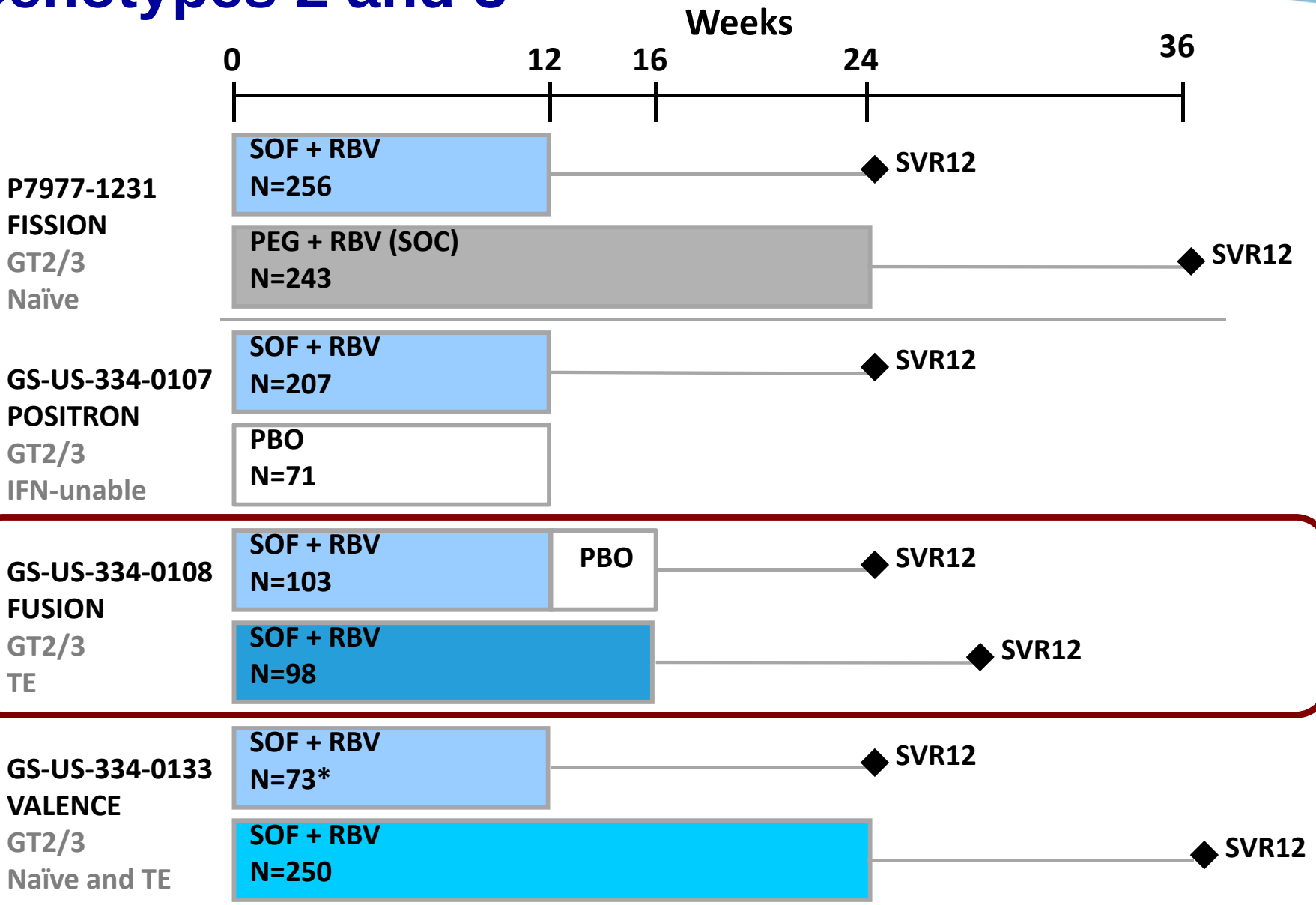


N=Number of subjects; SOC=Standard of care; PBO=Placebo; *N represents GT2 subjects only

POSITRON: GT 2/3 IFN-Unable SVR12 and Relapse Rates

	SOF+RBV 12 Weeks N=207	Placebo 12 Weeks N=71
Overall SVR12	**78%**	**0%**
Treatment Difference (95% CI)	78% (72%, 83%)	
GT 2	**93%** (101/109)	0% (0/34)
GT 3	**61%** (60/98)	0% (0/37)
Overall Relapse Rate	**20% (42/205)**	**-**
GT 2	**5%** (5/107)	-
GT 3	**38%** (37/98)	-

Phase 3 Trial Designs: Genotypes 2 and 3

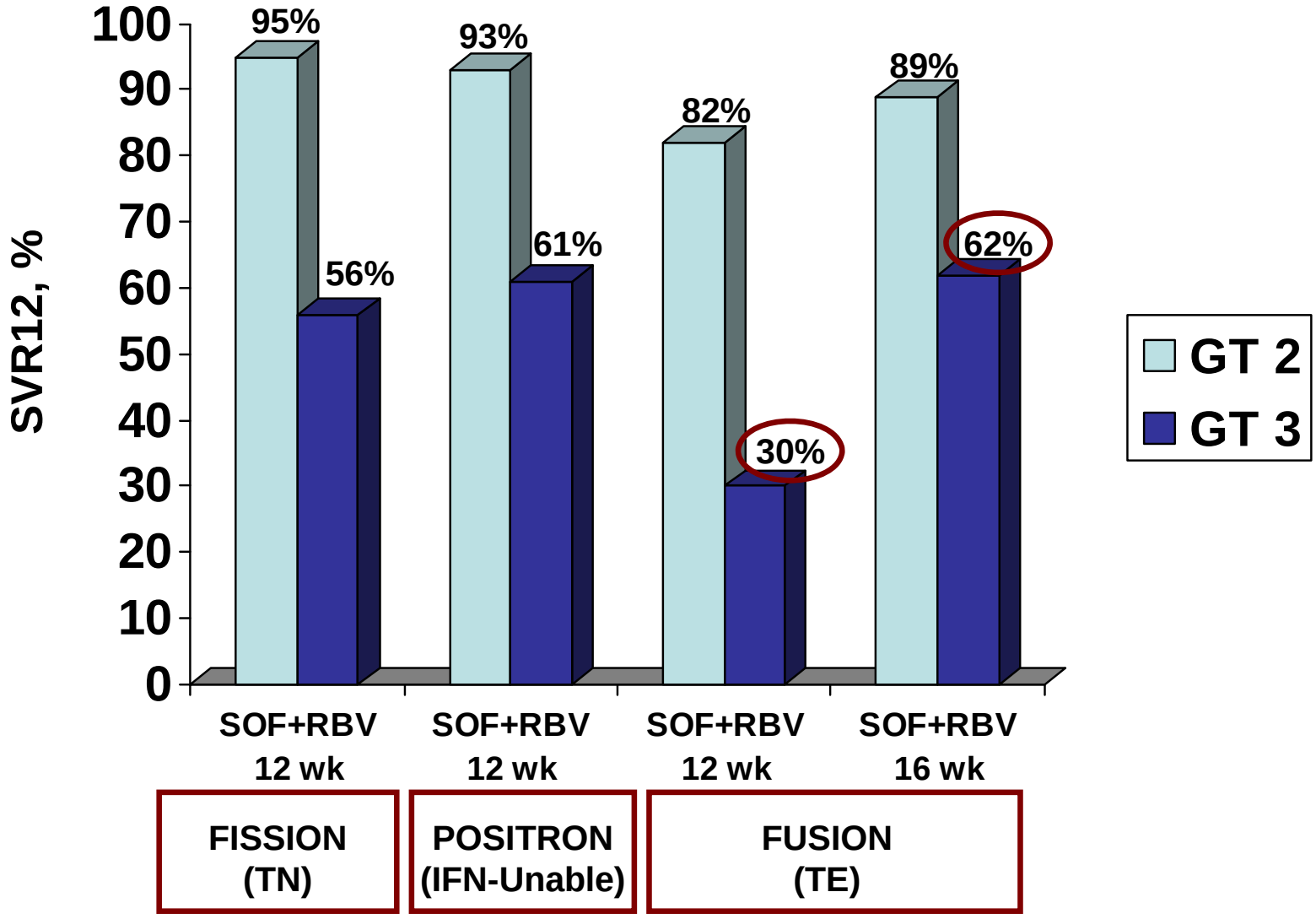


N=Number of subjects; SOC=Standard of care; PBO=Placebo; *N represents GT2 subjects only

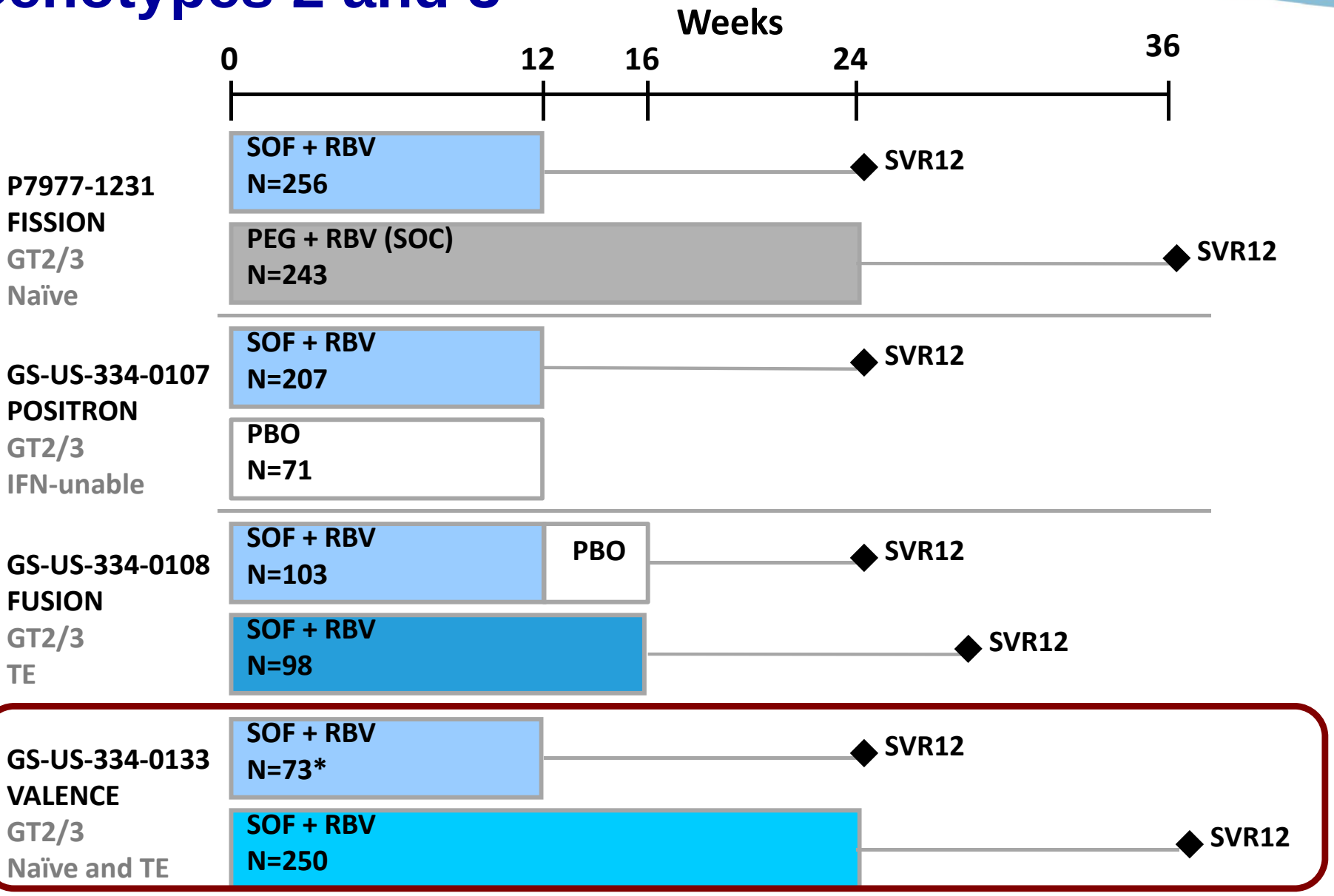
FUSION: GT 2/3 Treatment-Experienced SVR12 and Relapse Rates

	SOF+RBV 12 Weeks N=103	SOF+RBV 16 Weeks N=98
Overall SVR12	**50%**	**71%**
Treatment difference (95% CI)	-22% (-35%, -9%)	
GT 2	**82%** (32/39)	**89%** (31/35)
GT 3	**30%** (19/64)	**62%** (39/63)
Overall Relapse Rate	**48% (49/103)**	**29% (28/98)**
GT 2	**18%** (7/39)	**11%** (4/35)
GT 3	**66%** (42/64)	**38%** (24/63)

Difference in SVR12: GT 2 and GT 3



Phase 3 Trial Designs: Genotypes 2 and 3

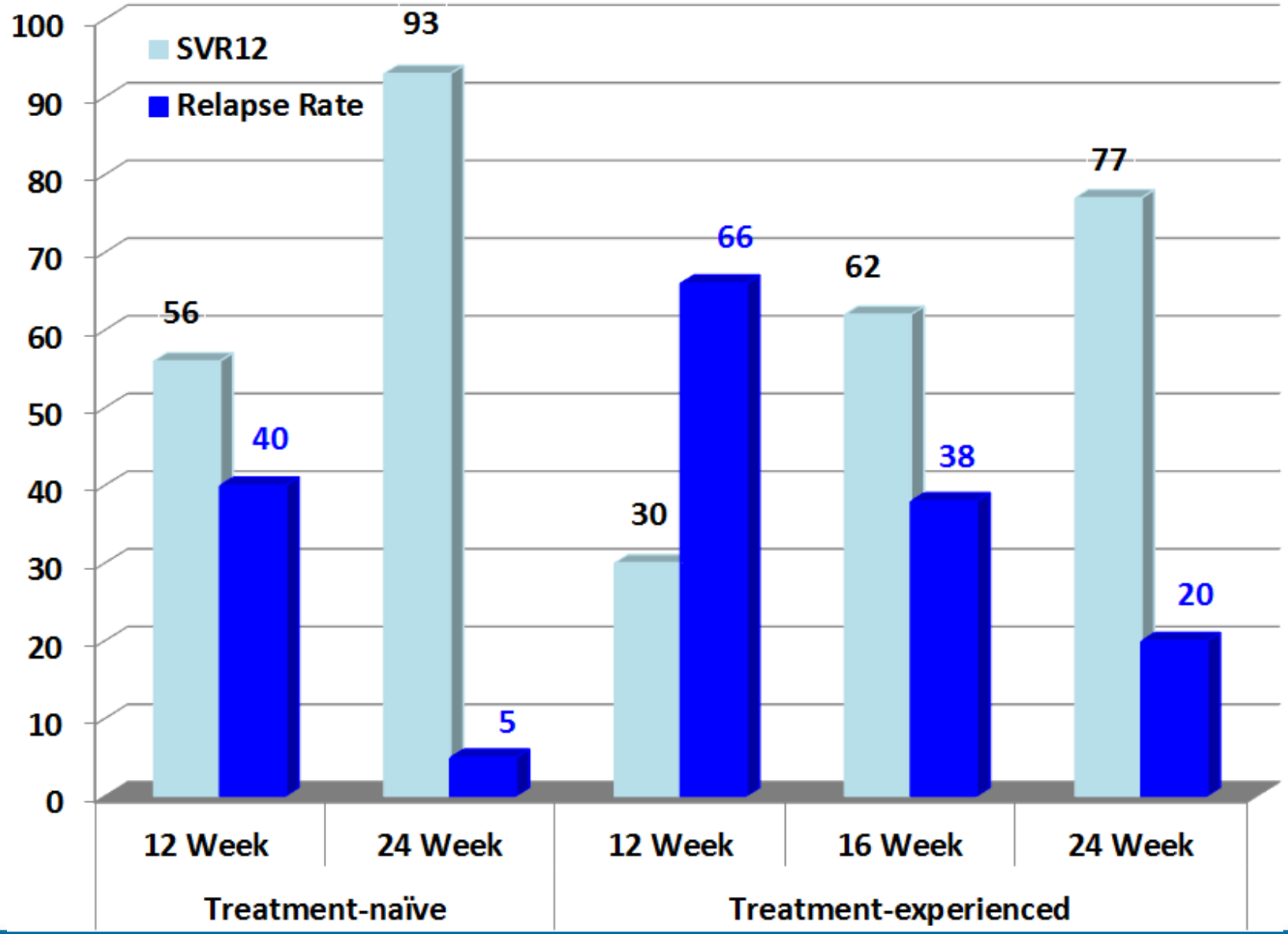


N=Number of subjects; SOC=Standard of care; PBO=Placebo; *N represents GT2 subjects only

VALENCE: GT 2/3
SVR12 and Relapse Rates

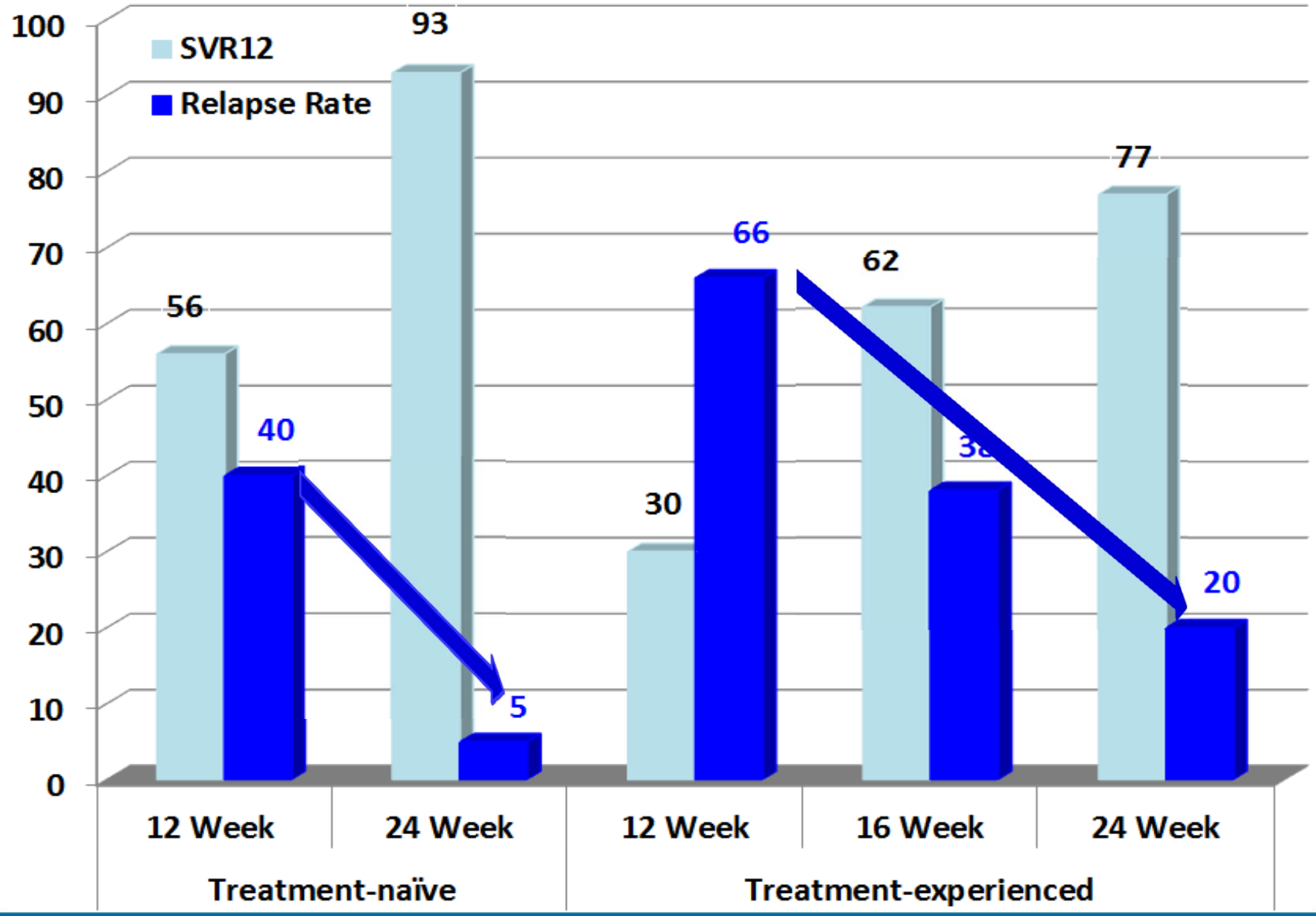
	GT 2 SOF+RBV 12 Weeks N=73	GT 3 SOF+RBV 24 Weeks N=250
Overall SVR12	**93%**	**84%**
Treatment-Naïve	**97%** (31/32)	**93%** (98/105)
Treatment-Experienced	**90%** (37/41)	**77%** (112/145)
Overall Relapse Rate	**7%** (5/73)	**14%** (34/249)
Treatment-Naïve	**3%** (1/32)	**5%** (5/105)
Treatment-Experienced	**10%** (4/41)	**20%** (29/144)

Genotype 3: SVR12 & Relapse Rate

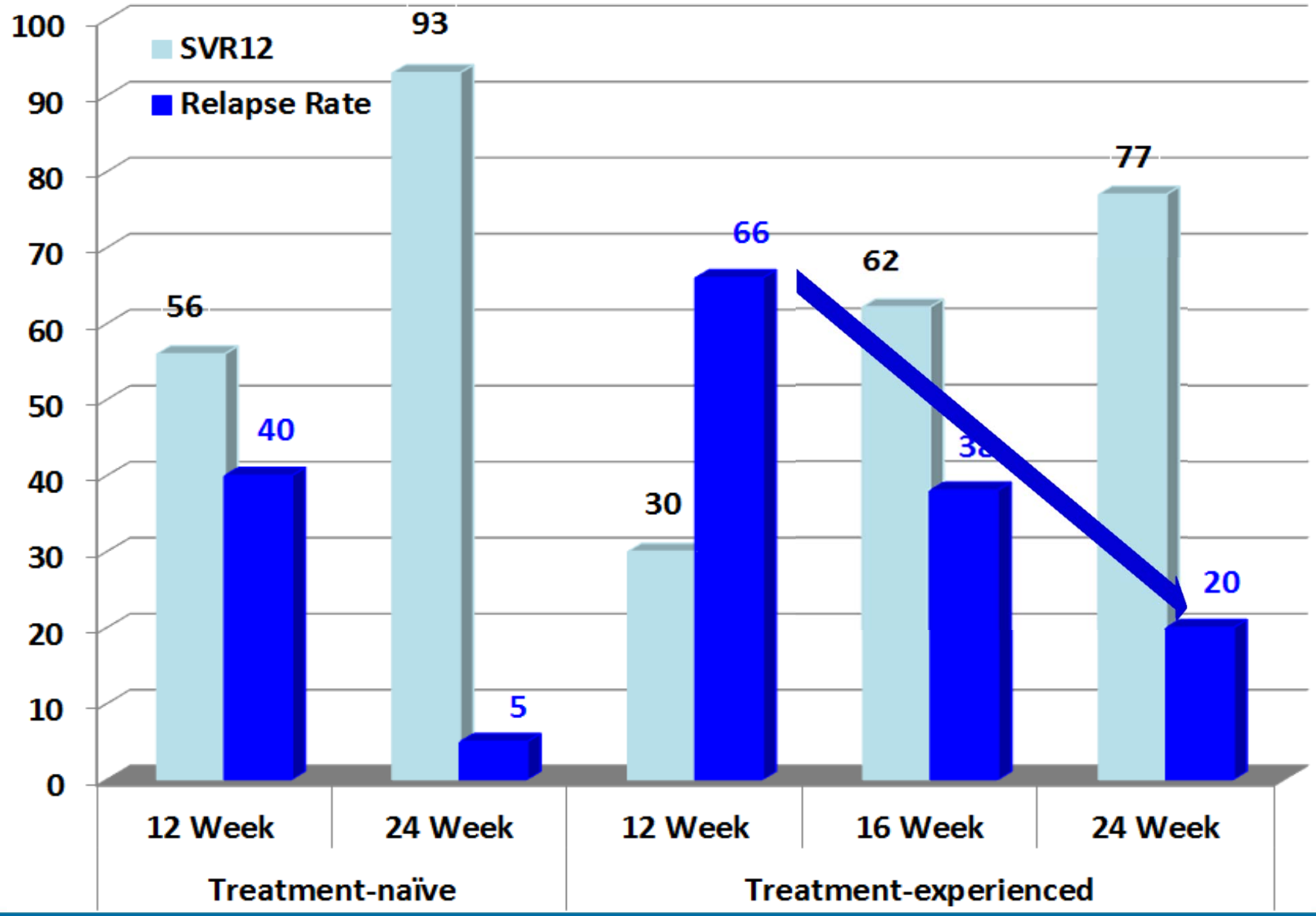


16

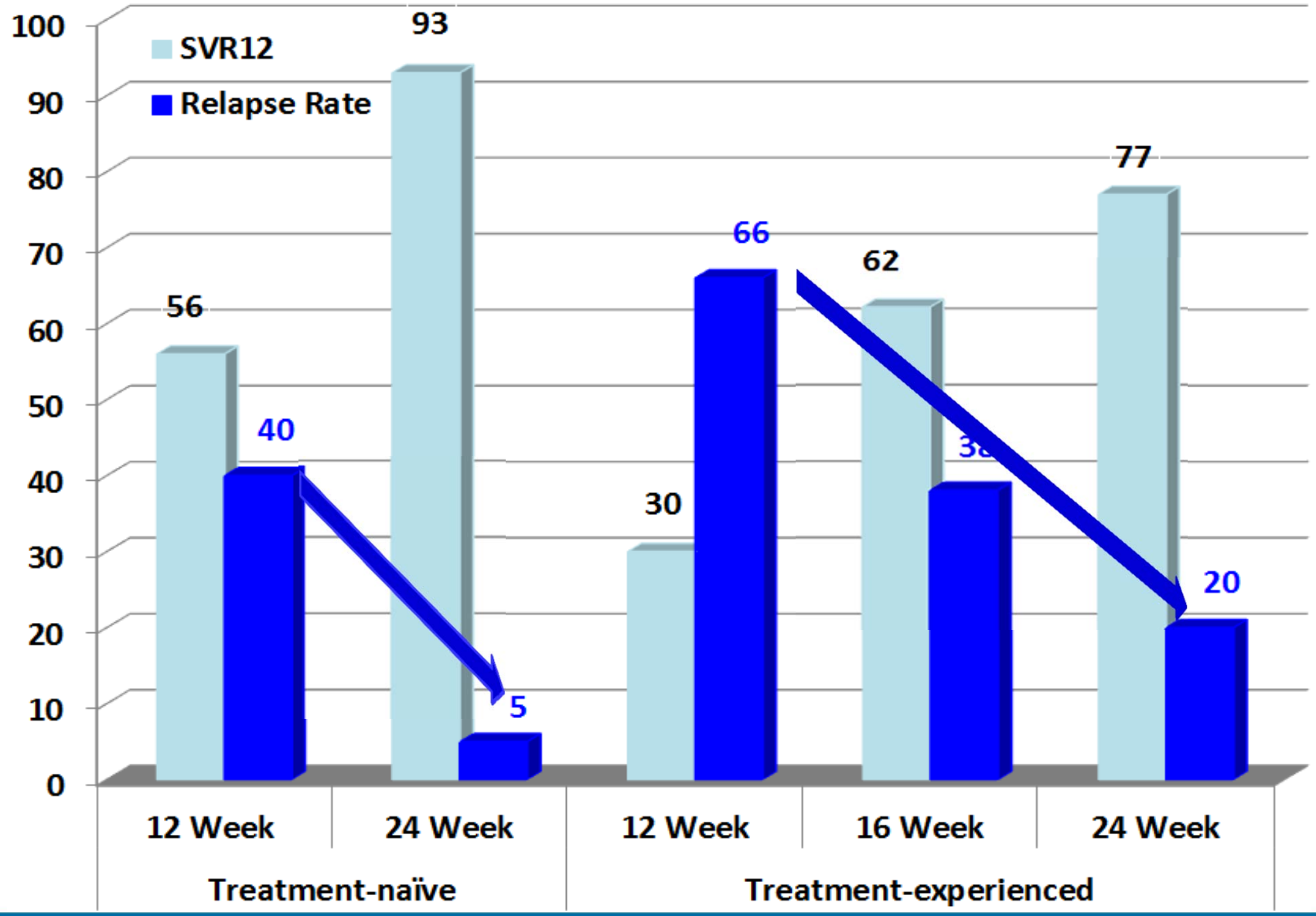
Genotype 3: SVR12 & Relapse Rate



Genotype 3: SVR12 & Relapse Rate



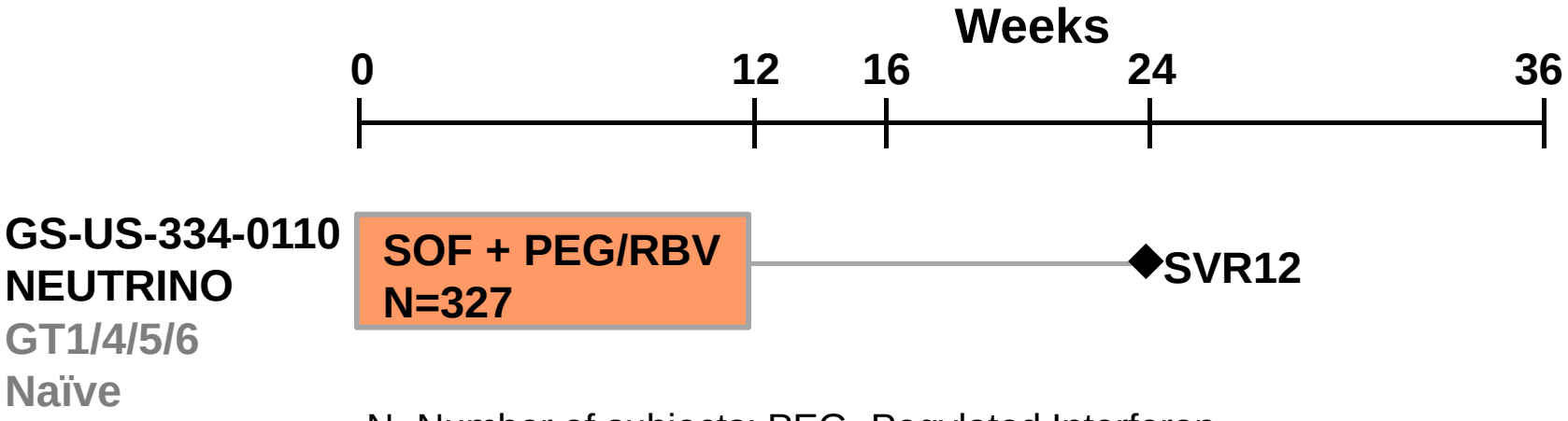
Genotype 3: SVR12 & Relapse Rate



Genotypes 1, 4, 5 and 6

Phase 3 Trial Design: GT 1, 4, 5, 6

Trial Name	Population	Regimen* and Duration
GS-US-334-0110 (NEUTRINO)	Treatment-Naïve	SOF+PEG/RBV 12 Weeks



N=Number of subjects; PEG=Pegylated Interferon

*SOF (400 mg/day) + PEG (180 μg/week) + RBV (1000 or 1200 mg/day)

NEUTRINO: GT 1, 4, 5, 6 Treatment-Naive SVR12

	SOF+PEG/RBV 12 wk N=327
Overall SVR12	**90% (295/327)**
GT 1	89% (261/292)
GT 1a	92% (206/225)
GT 1b	82% (54/66)
GT 4	96% (27/28)
GT 5*	100% (1/1)
GT 6*	100% (6/6)

*Available data on subjects with genotype 5 or 6 HCV infection is limited

Efficacy Summary: Phase 3 Trials

- **Genotype 2**: SOF+RBV 12 week duration
  - Treatment-naïve: 93-97%
  - Treatment-experienced: 82-90%
- **Genotype 3**: SOF+RBV 24 week duration
  - Treatment-naïve: 93%
  - Treatment-experienced: 77%
- **Genotypes 1 and 4**: SOF+PEG/RBV 12 week duration
  - GT 1 treatment-naïve: 89%
  - GT 4 treatment-naïve: 96%

Pre-Transplant Population

Pre-Transplant Population

- Recurrence of HCV infection after liver transplantation is almost universal
- Rate of fibrosis progression is accelerated compared to non-transplant HCV patients with approximately 10-25% developing cirrhosis within 5-10 years of transplantation[1]
- No approved therapies to prevent recurrence of HCV infection post-liver transplant
- Represents an area of unmet medical need

[1] Burra P. Seminars in Liver Disease 2009

P7977-2025: Pre-Transplant Trial

- Ongoing Phase 2 trial of SOF+RBV in HCV subjects (GT1-6) with hepatocellular carcinoma (HCC)
  - meeting the Milan criteria[1] prior to undergoing liver transplantation (*with anticipated time to transplant within one year*)
- Listed for liver transplant
  - MELD score of < 22 (HCC-weighted MELD score of ≥ 22)
  - Child-Pugh Turcotte (CPT) score ≤ 7
- Treatment duration was for a maximum of 24 weeks (*later extended to 48 weeks*), or until transplant, whichever comes first

[1] Milan criteria were defined as the presence of a tumor 5 cm or less in diameter in subjects with single hepatocellular carcinoma and no more than three tumor nodules, each 3 cm or less in diameter, in subjects with multiple tumors. There should be no extrahepatic manifestations of the cancer and no evidence of vascular invasion of the tumor.

P7977-2025: Pre-Transplant Trial Interim Efficacy Results

- Prevention of HCV recurrence post-transplant determined by a sustained post-transplant virological response (HCV RNA < LLOQ) at 12 weeks post-transplant (pTVR12).

Post-Transplant Virologic Response at Week 12

HCV Genotype	SOF+RBV
Overall pTVR12, % (n/N)	**64% (23/36)**
GT 1a	62% (8/13)
GT 1b	46% (6/13)
GT 2	100% (5/5)
GT 3	75% (3/4)
GT 4	100% (1/1)

Median time to transplant was 21 weeks (range: 2-42 weeks)

Summary of Pre-Transplant Data

- Subpopulation of pre-transplant patients eligible for a transplant due to upgrade in MELD scores due to HCC
- Demonstrated efficacy in a limited number of subjects (pTVR12 of 64%, 23/36)
- Optimal duration of treatment has not been determined
- Higher rates of SAEs, Grade 3 or 4 AEs, and deaths were reported in this pre-transplant population compared to the Phase 3 trials
- Addresses an unmet medical need

Safety Profile

Overall Summary of Adverse Events (Integrated Data)

	Placebo 12 Weeks POSITRON	SOF+RBV 12 Weeks FISSION, POSITRON, FUSION	SOF+RBV 24 Weeks VALENCE	SOF+PEG/RBV 12 Weeks NEUTRINO
	N=71 n (%)	**N=566** n (%)	**N=250** n (%)	**N=327** n (%)
Any Adverse Event (AE)	55 (78)	496 **(88)**	228 **(91)**	310 (95)
Serious AE	2 (2.8)	22 **(3.9)**	10 **(4.0)**	4 (1.2)
Grade 3 or 4 AE	1 (1.4)	41 **(7.2)**	17 **(6.8)**	48 (14.7)
AE Leading to Permanent Discontinuation from Any of the Study Drugs	3 (4.2)	9 **(1.6)**	1 **(0.4)**	8 (2.4)

Serious Adverse Events in Phase 3 Trials

- Incidence of SAEs was comparable between the SOF+RBV 12 Week group (3.9%) and SOF+RBV 24 Week group (4%)
- Incidence of SAEs that were considered related to the study drug by the investigators was very low (<1%)
  - The investigator's causality assessment for relatedness seems reasonable for the observed SAEs.
- There was no apparent clustering of SAEs observed within system organ classes (SOCs)
- The only SAE seen in ≥ 3 subjects in SOF+RBV group was: Malignant hepatic neoplasm

Evaluation of Cardiac Disorders Sofosbuvir-Treated Subjects

- No cases of cardiomyopathy reported
- No serious or severe cardiac AEs reported
- No treatment discontinuations due to cardiac AEs
- No clustering of cardiac-related AEs
- Based on the review of the submitted data, no obvious safety issue related to cardiac toxicity has been identified to date.

Safety Summary

- Sofosbuvir regimens (in combination with RBV or in combination with PEG/RBV) were well tolerated in all patient populations studied
- No clustering or trends of any specific adverse events were noted
- At this time no safety concerns specific to cardiac toxicity associated with sofosbuvir use have been identified

Clinical Virology

Next Generation Sequencing Data

Of 982 subjects in the SOF+RBV or SOF+PEG+RBV groups of Phase 3 Trials:

Clinical Trial	Subjects with NGS Data	NGS Raw Data Files
P7977-1231 (FISSION)	78	308
GS-US-334-0107 (POSITRON)	41	115
GS-US-334-0108 (FUSION)	76	189
GS-US-334-0110 (NEUTRINO)	29	64
Totals	**224**	**676**

Treatment-Emergent NS5B Substitutions: Treatment Failures

- **S282T**
  - GT2b relapser (12 week SOF monotherapy)
- **L159F**
  - Previously identified HCV NS5B nucleotide inhibitor resistance-associated substitution[1]
  - 6 GT3a relapsers
- **V321A**
  - 5 GT3a relapsers

[1] Tong et al., 63rd AASLD, Nov 9-13, 2012

Treatment-Emergent NS5B Substitutions: Treatment Failures

+ Pre-Transplant Trial P7977-2025 (SOF+RBV)

- **S282T or R**

– *GT 2b relapser (12 week SOF monotherapy)*

– S282R+L320F[1]: GT 1a non-responder

- **L159F**

– *6 GT 3a relapsers*

– 2 GT 1a subjects (one breakthrough and one relapser)

– 1 GT 2b subject (breakthrough)

– Present at baseline in 4 GT 1b subjects who had breakthrough or relapsed post-transplant

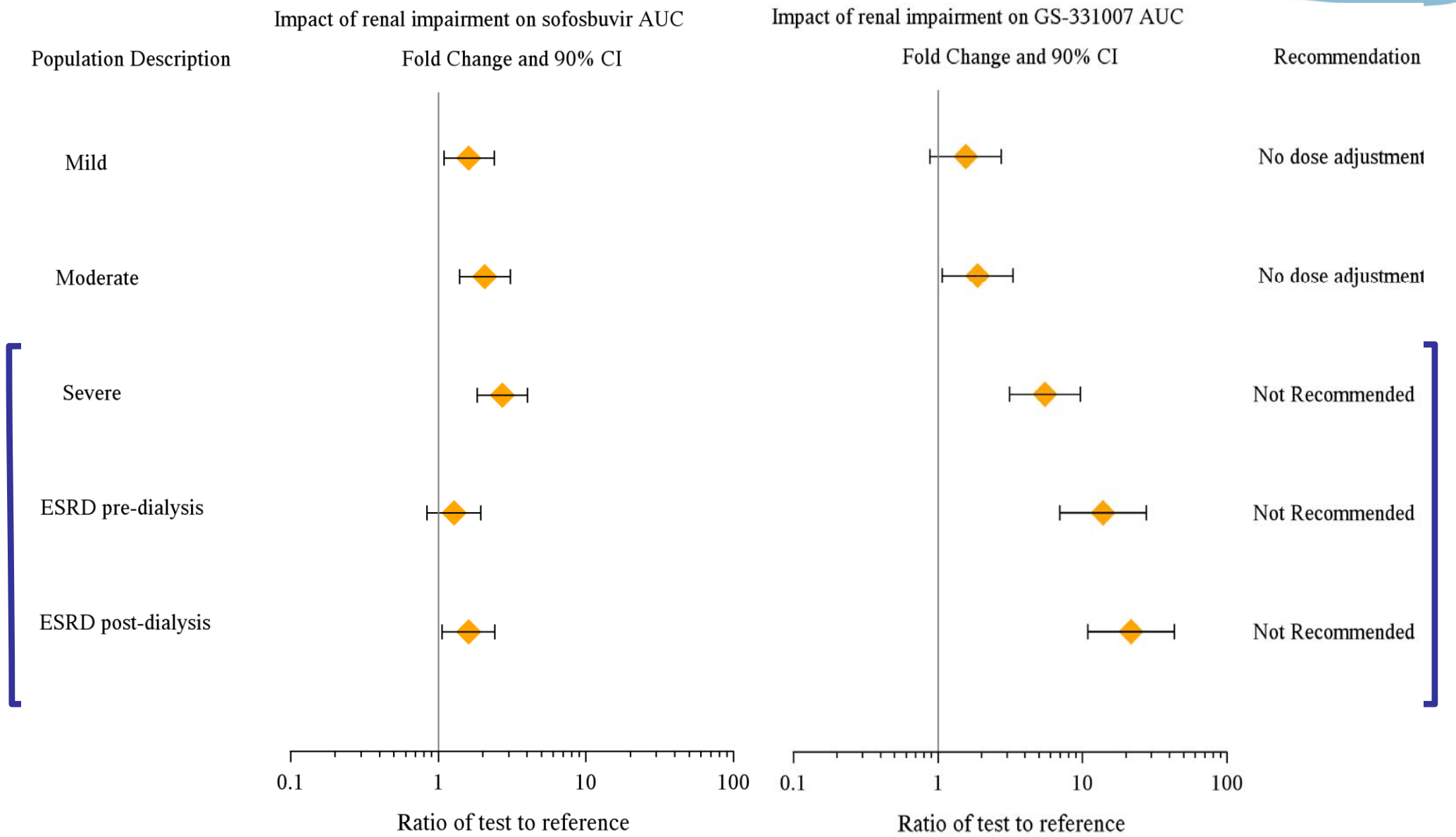
[1]Tong et al., 63rd AASLD, Nov 9-13, 2012

Resistance Summary

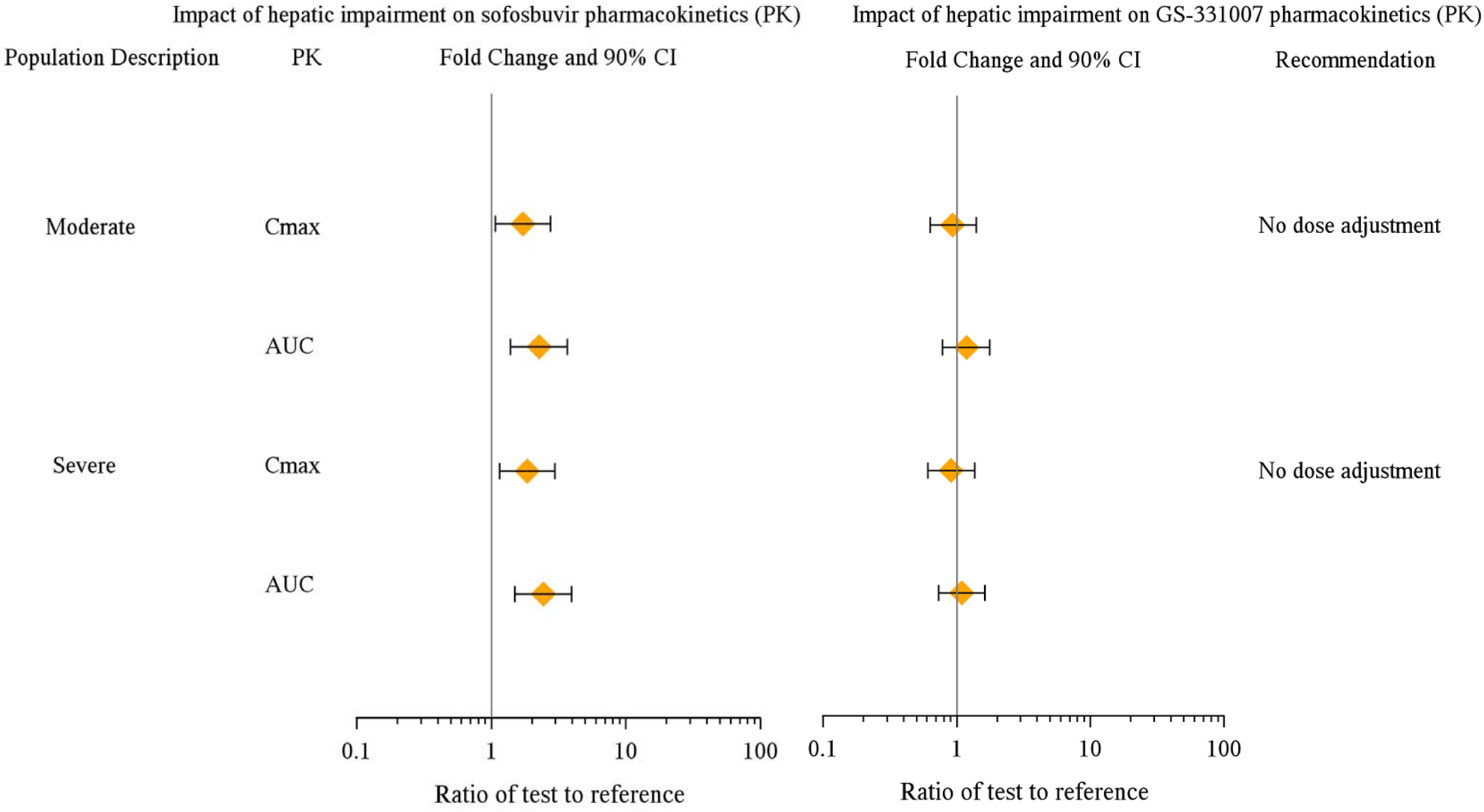
- Overall, these results indicate that when sofosbuvir is not used as part of an optimal regimen or duration, resistance may emerge.
- Evidence of genotypic resistance in breakthroughs and relapses
  - SOF Monotherapy Relapse: S282T with mean 13.5-fold reduced susceptibility to SOF
  - SOF+RBV GT1a nonresponder: S282R+L320F
  - Breakthroughs/Relapses in multiple studies and genotypes: L159F and V321A (no detectable shift in phenotypic susceptibility to sofosbuvir)

Clinical Pharmacology

Recommended for Mild and Moderate Renal Impairment



No Dose Adjustment for Any Degree of Hepatic impairment



Drug Interactions: Potential Effect of Other Drugs on Sofosbuvir

Drug	Effect on Sofosbuvir	Recommendation
P-gp or BCRP Inducers		
Rifampin St. John's wort Tipranavir Rifabutin Rifapentine Anticonvulsants	↓ Sofosbuvir	**Should not be coadministered**

Drug Interactions: No Clinically Significant Effect

Drug	Effect on Sofosbuvir, Metabolite, or Interacting Drug	Recommendation
Darunavir/ritonavir Emtricitabine Efavirenz Raltegravir Rilpivirine Tenofovir DF Methadone Tacrolimus Cyclosporine*	↔ Sofosbuvir ↔ GS-331007 (SOF metabolite) ↔ Interacting drug	**Can coadminister with no dose adjustment of either drug**

*Cyclosporine increased the concentrations of sofosbuvir and GS-331007; however, the increase was not considered clinically significant.

Clinical Pharmacology Summary

- No dose adjustment needed for sofosbuvir in patients with mild or moderate renal impairment.
- Sofosbuvir can be used in patients with hepatic impairment *(any degree)* with no dose adjustment.
- There is the potential for a reduction in the efficacy of sofosbuvir when it is coadministered with P-gp or BCRP inducers.
- Drug interaction studies conducted to date have demonstrated no clinically significant changes for either sofosbuvir or the interacting drug.

Conclusions

- Sofosbuvir in combination with ribavirin provides the first, all-oral interferon-free regimen for CHC patients with genotype 2 or 3 HCV infection
- Sofosbuvir in combination with pegylated interferon and ribavirin provides improved efficacy, and shorter treatment duration for CHC patients with genotype 1 or 4 HCV infection
- Sofosbuvir and ribavirin regimen provides a therapeutic option for CHC patients with HCC awaiting liver transplantation thus addressing an unmet need
- No major safety issues associated with sofosbuvir use have been identified to date

Use of Sofosbuvir in Genotype 1 PEG/RBV Treatment-Experienced Population

Jeffry Florian PhD and Karen Qi PhD
on behalf of the
Sofosbuvir Review Team

Antiviral Drugs Advisory Committee Meeting
October 25, 2013

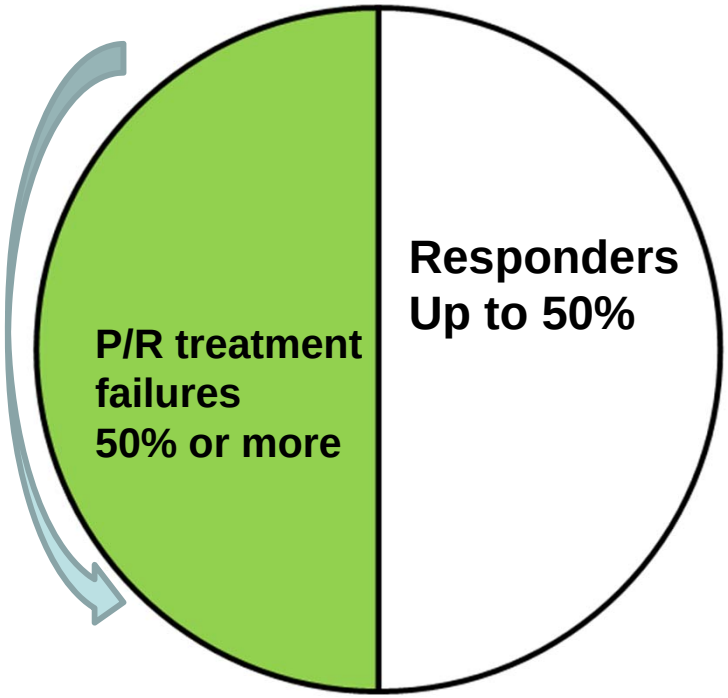
Genotype 1 PEG/RBV Treatment-Experienced Population

Does the high SVR rate in the treatment-naïve (TN) population provide evidence to support use of sofosbuvir in combination with PEG/RBV for treatment of CHC in patients with GT 1 infection who are nonresponders to a prior course of PEG/RBV?

- SVR12 rate of 89% was demonstrated with a 12-week SOF+PEG/RBV regimen in HCV GT 1 TN subjects (NEUTRINO)
- 12-week SOF+PEG/RBV regimen was not specifically evaluated in HCV GT 1 treatment-experienced (TE) subjects in the sofosbuvir development program

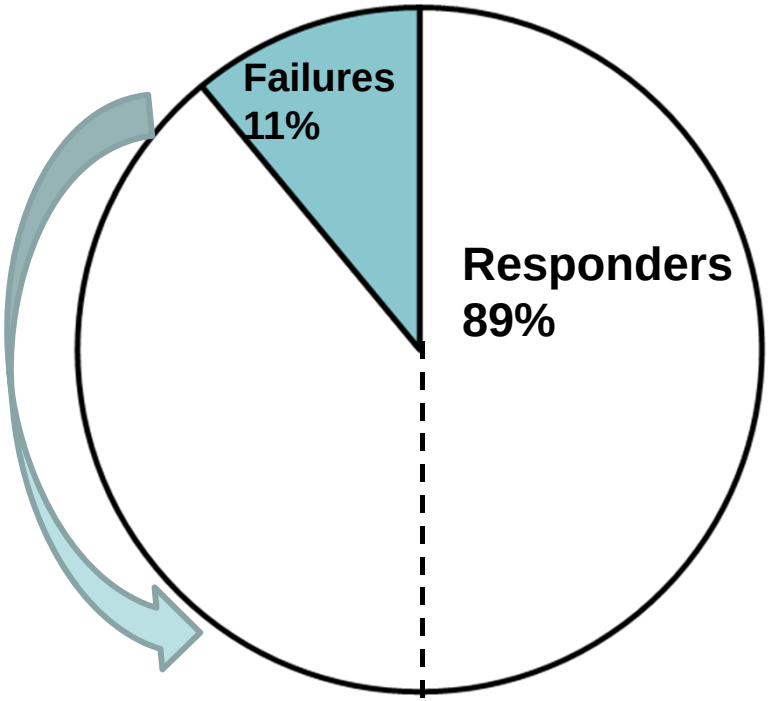
Predicted SVR in GT 1 PEG/RBV TE Population

Historical PEG/RBV Response



Subjects classified as PEG/RBV treatment failures*

NEUTRINO Response Rates

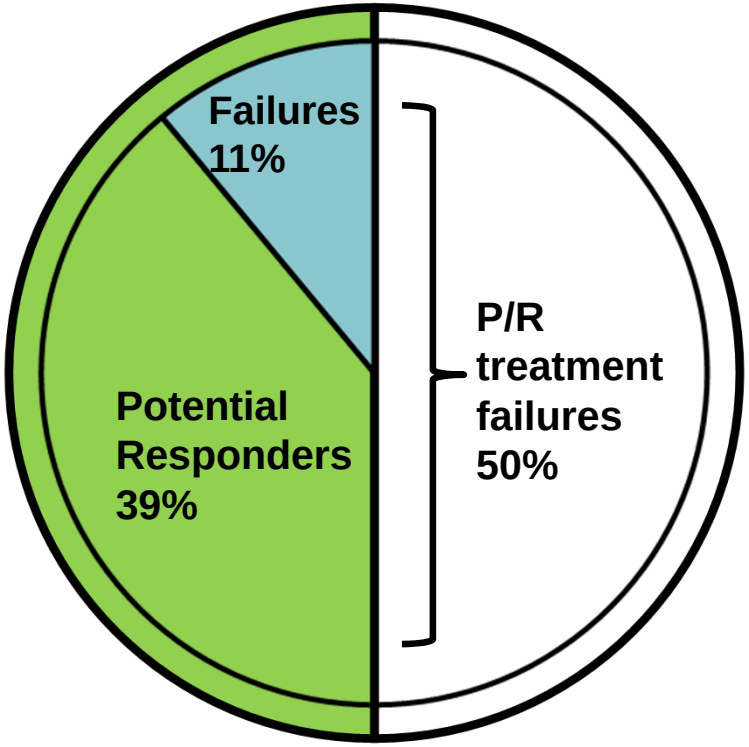


Response rates in these subjects most likely contributed to overall increase in SVR

* Includes relapsers, partial responders, null responders, and discontinuations

Predicted SVR in GT 1 PEG/RBV TE Population

Historical PEG/RBV Response NEUTRINO Response Rates



Predicted SVR in GT 1 P/R TE Population = 78% (39/50)

Baseline Factors Predictive of Lower PEG/RBV Response[1] in GT 1

- High baseline HCV RNA
- Fibrosis score F3 or F4
- Steatosis
- Pretreatment fasting glucose ≥ 5.6 mmol/L
- Pretreatment ALT level >upper limit of normal
- Race
  - African Americans

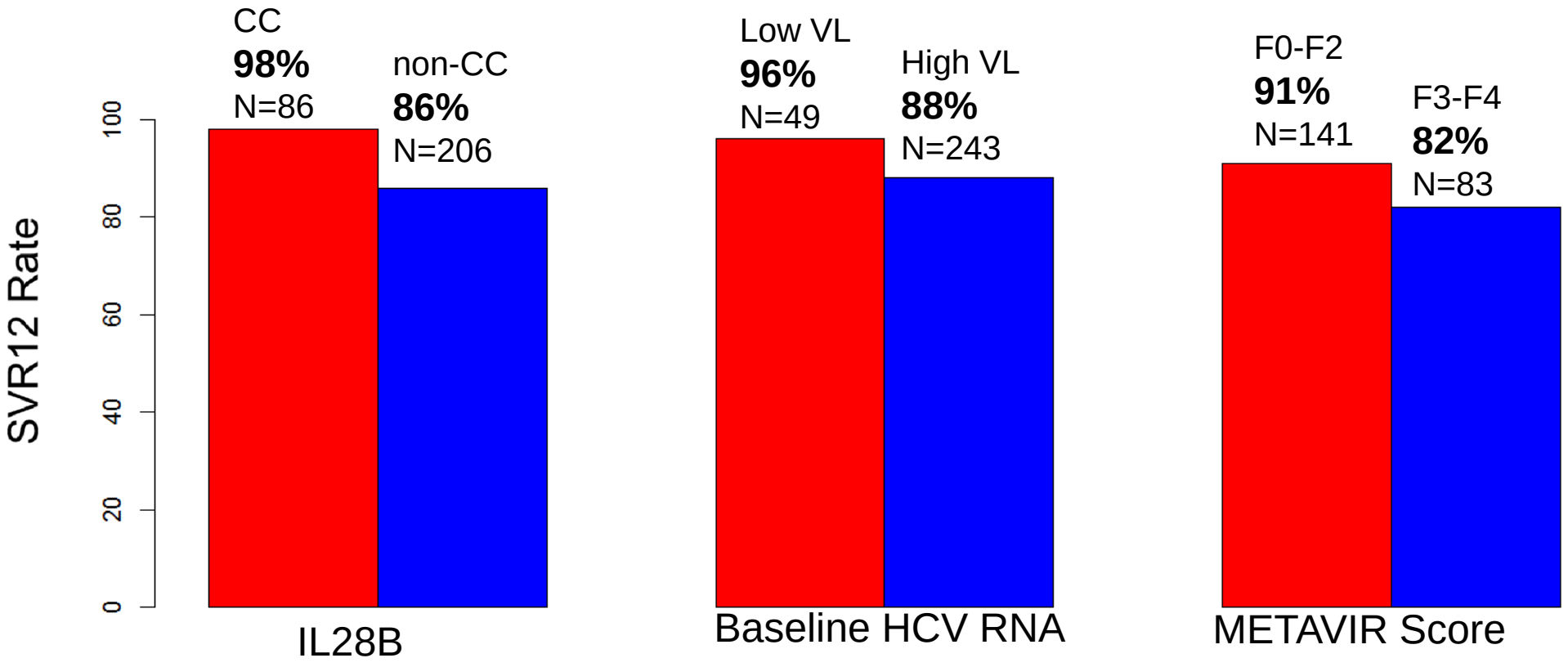
IL28B

Subsequent GWAS identified a host polymorphism associated with response to treatment: IL28B (linked with race)[2]

Selected Baseline Predictive Factors: FDA Analyses

- These factors were previously identified to predict response rates in harder-to-treat GT 1 TN subjects[1, 2, 3, 4, 5]
  - IL28B non-CC
  - High baseline HCV RNA Viral Load
  - METAVIR F3-F4
- Based on these baseline predictors, accrued knowledge has shown overlapping SVR rates between the harder-to-treat treatment-naïve population and documented partial/null responders.
  - Harder-to-Treat Treatment-Naïve: 43-51%
  - Partial and Null Responders: 44-59%

NEUTRINO: SVR12 Rates in Harder-to-Treat GT 1 TN Subjects



Non-CC/High baseline HCV viral load/F3-F4

71% (37/52)

95% CI: (57%, 83%)

Considerations and Limitations

Considerations	Limitations
• High response rate observed in GT 1 TN subjects	• No available data in GT 1 PEG/RBV TE subjects
• FDA analyses predict high SVR rates in GT 1 PEG/RBV TE population	• Analyses based on assumptions

- May provide therapeutic option for GT 1 PEG/RBV TE population
- Shorter treatment duration may provide an improved safety profile

References

1. IDEAL Study Team, Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 361(6):580-93 (2009).

2. Ge, D., Fellay J., Thompson A.J., Simon J.S. et al, Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 461(7262):399-401 (2009).

3. Ghany, M. G., Strader, D. B., Thomas, D. L., Seeff, L. B. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 49, 1335–1374 (2009).

4. Ghany M.G., Nelson D.R., Strader D.B., Thomas D.L., Seeff, L.B. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases; American Association for Study of Liver Diseases Hepatology 54(4), 1433-44 (2011).

5. HALT-C Trial Group, Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. Gastroenterology 126, 1015–1023 (2004).

Acknowledgements

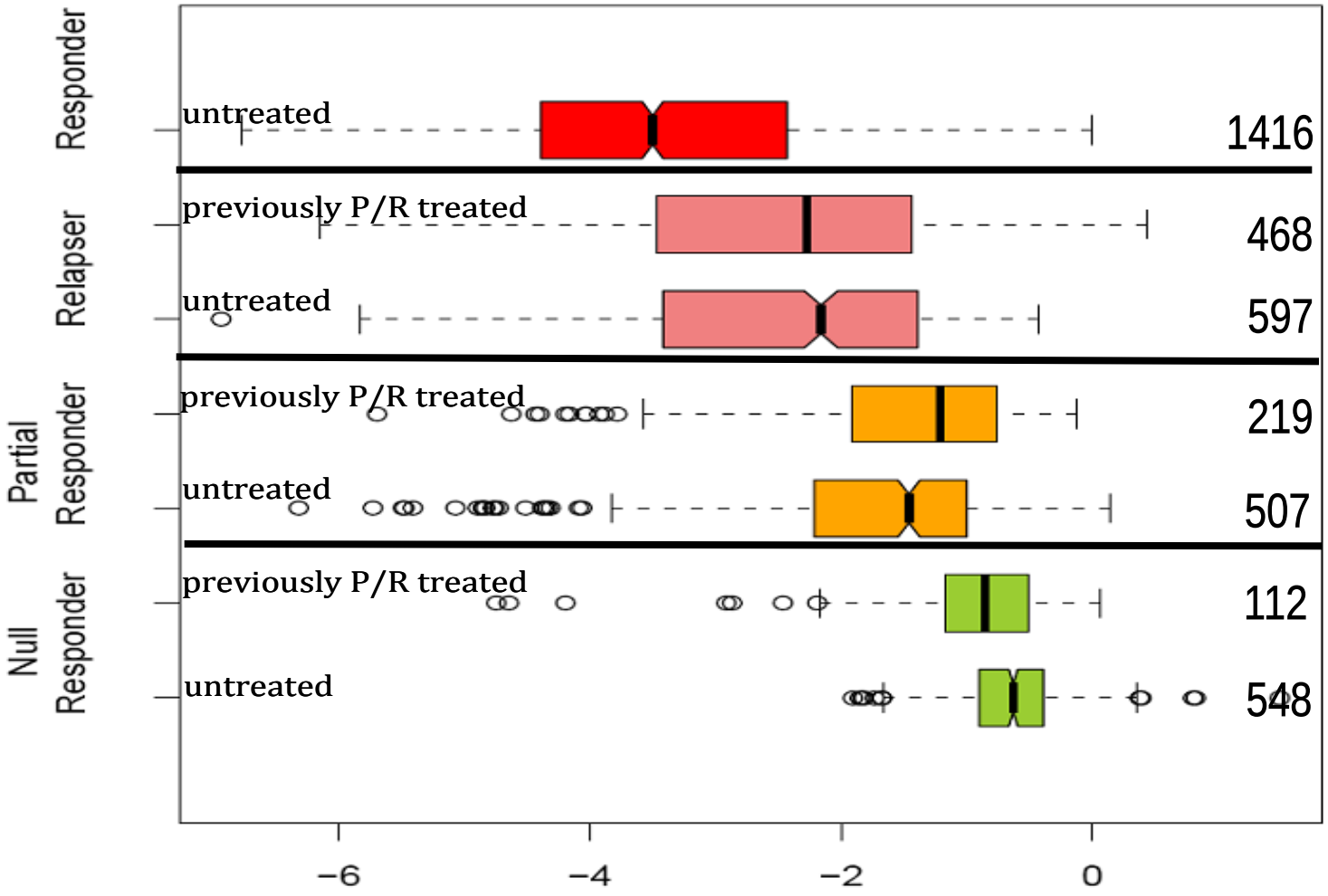
- Edward Cox, M.D., M.P.H.
- Debra Birnkrant, M.D.
- Jeffrey Murray, M.D., M.P.H.
- Sarah Connelly, M.D.
- Kimberly Struble, Pharm.D.
- Kendall Marcus, M.D.
- Dionne Price, Ph.D.
- Guoxing Soon, Ph.D.
- Wen Zeng, Ph.D.
- Karen Qi, Ph.D.
- Julian O'Rear, Ph.D.
- Lisa Naeger, Ph.D.
- Eric Donaldson, Ph.D.
- John Lazor, Pharm.D.
- Michael Pacanowski, Pharm.D., M.P.H.
- Shirley Seo, Ph.D.
- Jenny Zheng, Ph.D.
- Yaning Wang, Ph.D.
- Jeffry Florian, Ph.D.
- Sarah Dorff, Ph.D.
- Hanan Ghantous, Ph.D., DABT
- Christopher Ellis, Ph.D.
- Rapti Madurawe, Ph.D.
- Stephen Miller, Ph.D.
- George Lunn, Ph.D.
- Fuqiang Liu, Ph.D.
- Minerva Hughes, Ph.D.
- Steven Donaldson, Ph.D.
- Antonie El Hage, Ph.D.
- Mahesh Ramanadham, Pharm.D.
- Krishna Gosh, Ph.D.
- David Roeder, M.S.
- Karen Winestock
- Linda Onaga, M.P.H.
- Sohail Mosaddegh, Pharm.D.
- Office of Compliance
- Office of Regulatory Affairs
- Office of Surveillance and Epidemiology
- Division of Drug Medication Error and Analysis
- Office of Prescription Drug Promotion
- Computational Science Center
- Timothy J. Kropp, Ph.D.

Back-Up Slides Shown

"Reversion" of NS5B Substitutions

- S282T (GT2b SOF monotherapy subject) emerged at Week 4 post-treatment and was no longer detected at Week 12 post-treatment.
- In one breakthrough subject, L159F was present at a frequency of 9.5% at Post-Transplant Week 1 and this dropped to 1.2% by Post-Transplant Week 2
- Many of the GT3a relapser samples were collected weeks after termination of treatment
  - Possible that F159 was present in the relapse samples while on-treatment, but rapid displacement would result in no detectable F159 in samples that were taken too long after relapse (>2 weeks).

Similar Virologic Response at Week 4 with First or Second PR treatment (pooled analysis)



E-10

Liu *et al. CID 2012*